II. REMARKS

Formal Matters

Claims 1, 3, 5, 7, and 9-22 are pending after entry of the amendments set forth herein.

Claims 1, 3, 5, 7, 14, 15, and 20-22 were examined and were rejected. Claims 9-13 and 16-19 were withdrawn from consideration.

The specification is amended to add material incorporated by reference, as requested in the Office Action. No new matter is added by this amendment.

New Figures 5A and 5B are added, to include material incorporated by reference. No new matter is added.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Withdrawal of previous rejections

Applicants note that the following rejections, raised in the October 23, 2003 Office Action, were not reiterated in the April 20, 2004 Office Action, and are presumed to have been withdrawn: 1) rejection of claims 1-4, 14, and 15 under 35 U.S.C.§112, first paragraph; 2) rejection of claims 1, 2, 14, and 15 under 35 U.S.C.§112, second paragraph; and 3) rejection of claims 1-4, 14, and 15 under 35 U.S.C.§103(a).

Rejection under 35 U.S.C.§112, first paragraph

Claims 1, 3, 5, 7, 14, 15, and 20-22 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking adequate written description. Claims 1, 3, 5, 7, 14, 15, and 20-22 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

Written description

The Office Action stated that "the claimed embodiment of a Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4 lacks a written description." Office Action, page 4. The Office Action stated that the skilled artisan could not envision such equivalent positions, and therefore, conception is not achieved until reduction to practice has occurred. Applicants respectfully traverse the rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention. As Applicants indicated in the specification, mouse apoE, as well as apoE of at least nine other species, contains a Thr residue at a position equivalent to Arg-61 of human apoE4. Specification, paragraph 0009. The specification provided a reference to Weisgraber et al. ((1994) *Adv. Protein Chem.* 45:240-302; "the Weisgraber reference"). The Weisgraber reference includes the full amino acid sequences of apoE from various species, aligned with human apoE4. The Weisgraber reference, page 252, Figure 1. The Weisgraber reference was readily available to those skilled in the art as of the March 16, 2001 priority date of the instant application. Indeed, the amino acid sequences provided in the Weisgraber reference were all available to the public by 1991. In particular, the amino acid sequence of mouse apoE was published in 1985; and the amino acid sequence of human apoE4 was published in 1982. The Weisgraber Reference, legend to Figure 1. Those skilled in the art would have appreciated that Applicants aligned the amino acid sequence of mouse apoE and human apoE4 and identified the equivalent to Arg-61, using a standard alignment method or computer program. Thus, those skilled in the art would have appreciated that Applicants were in possession of the claimed invention as of the priority date of the instant application.

Enablement

The Office Action stated that: 1) the specification fails to provide teachings or guidance with regard to the particular human sequence with amino acid 61 which would be used to identify the amino acid equivalent in the mouse sequence; and 2) the instant specification fails to enable the methods of utilizing the claimed transgenic mouse in methods of identifying agents that reduce a phenomenon associated with Alzheimer's Disease (AD).

1. The specification is enabling provides adequate guidance with regard to the human apoE4 amino acid sequence which would be used to identify the amino acid equivalent in the mouse sequence.

The Office Action stated that the specification fails to provide teachings or guidance with regard to the particular human sequence with amino acid 61 which would be used to identify the amino acid equivalent in the mouse sequence. However, as noted above, the specification states that mouse apoE, as well as apoE of at least nine other species, contains a Thr residue at a position equivalent to Arg-61 of human apoE4. Specification, paragraph 0009. The specification provided a reference to Weisgraber et al. ((1994) *Adv. Protein Chem.* 45:240-302; "the Weisgraber reference"). The Weisgraber reference

includes the full amino acid sequences of apoE from various species, aligned with human apoE4. The Weisgraber reference, page 252, Figure 1. The Weisgraber reference was readily available to those skilled in the art as of the March 16, 2001 priority date of the instant application. Indeed, the amino acid sequences provided in the Weisgraber reference were all available to the public by 1991. In particular, the amino acid sequence of mouse apoE was published in 1985; and the amino acid sequence of human apoE4 was published in 1982. The Weisgraber Reference, legend to Figure 1. Those skilled in the art could have readily aligned the amino acid sequence of mouse apoE and human apoE4 and identified the equivalent to Arg-61, using a standard alignment method or computer program, and arrived at the alignment as shown in the Weisgraber Reference.

The specification further states that the codon for the Thr-61 equivalent in the mouse apoE gene is located at the end of the third exon of the *apoE* gene, exactly as it is in the human gene. Specification, paragraph 00188.

Those skilled in the art, given the guidance in the specification, and the knowledge in the art (e.g., the Weisgraber reference), could have readily identified an amino acid in an apoE protein that is equivalent to Arg-61 of human apoE4. Accordingly, the instant specification complies with the enablement requirement of 35 U.S.C.§112, first paragraph.

The Office Action stated that the amino acid sequence of human apoE4 is considered essential subject matter; and stated that this subject matter has been improperly incorporated by reference. The Office Action stated that the Weisgraber reference was improperly incorporated by reference, because the specification does not particularly disclose the human apoE4 sequence and the alignment thereof. The Office Action required that Applicants amend the disclosure to include the material incorporated by reference.

As noted above, the specification provides ample guidance, in combination with the knowledge in the art (e.g., as exemplified by the Weisgraber reference), to identify an amino acid equivalent to human Arg-61.

Nevertheless, and solely in the interest of expediting prosecution, the specification is amended to include Figure 1 (numbered in the instant specification as Figures 5A and 5B), and the accompanying figure legend, from the Weisgraber reference. A sequence listing is also provided. The specification is amended to include the description of Figures 5A and 5B; the description of Figures 5A and 5B is taken

from the legend to Figure 1 in the Weisgraber reference.

As provided for under MPEP §608.01(p), the undersigned Applicants' representative hereby declares that the amendatory material added to the instant specification, i.e., new Figures 5A and 5B; the amendment to the specification to include the description of Figures 5A and 5B; and the amendment to the specification to include a sequence listing, consists of the same material incorporated by reference, i.e., the Weisgraber reference.

2. The specification provides adequate guidance for those skilled in the art to use a subject gene-modified mouse in a method to identify agents that reduce a phenomenon associated with AD.

The Office Action stated that the instant specification fails to enable the methods of utilizing the claimed transgenic mouse in methods of identifying agents that reduce a phenomenon associated with AD. The Office Action stated that the specification fails to provide a correlation between the phenotype of the claimed mice and AD. The Office Action stated that neither the specification nor the art at the time of filing provide a nexus between the phenotype of the claimed mice and a phenomenon associated with AD.

As a first note, Applicants point out that, while claims 1, 3, 5, 7, 14, 15, and 20-22 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement, on the basis that "the instant specification fails to enable the methods of utilizing the claimed transgenic mouse in methods of identifying agents that reduce a phenomenon associated with Alzheimer's Disease (AD)" (Office Action, page 8), claims 1, 3, 5, 7, and 20-22 are not directed to a method for identifying an agent that reduces a phenomenon associated with AD. Instead, claims 14 and 15 recite a method for identifying an agent that reduces a phenomenon associated with AD. Accordingly, Applicants will address this rejection as it might apply to claims 14 and 15.

The enablement requirement of 35 U.S.C.§112, first paragraph

The enablement requirement of 35 U.S.C.§112, first paragraph, refers to the requirement that the specification describe how to make and how to use the claimed invention. The test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosures in the patent application, coupled with information known in the art, without undue experimentation. A specification disclosure which contains a teaching of the manner and process of making and using an

invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Claim 14 recites a method for identifying an agent that reduces a phenomenon associated with AD, the method comprising contacting the gene-targeted mouse of claim 1 with a test agent; and determining the effect of the test agent on reducing a phenomenon associated with AD. Claim 15 depends from claim 14.

2a. The specification provides ample description for utilizing the claimed gene-targeted mouse in methods of identifying agents that reduce a phenomenon associated with AD.

The specification states that the invention provides non-human gene-targeted animal models for the study of apoE4-associated pathologies, wherein the endogenous apoE gene of the gene-targeted animal is genetically altered such that the encoded recombinant apoE polypeptide exhibits domain interaction; and that such animals serve as models for human apoE4 domain interaction. Specification, paragraph 0015. The specification states that such animals are useful in drug screening assays, e.g., to identify agents that reduce apoE4 domain interaction are identified by a change in a phenomenon associated with an apoE4-related neurological disorder, such as AD. Specification, paragraphs 0029, 0050, and 00108. The specification states that phenomena associated with AD include amyloid deposits, neuronal cell loss, and neurofibrillary tangles. Specification, paragraphs 0029 and 00128.

The specification describes how to determine whether a test agent reduces a phenomenon associated with AD. For example, the specification discusses immunohistological assays for the presence of neuritic plaques and neurofibrillary tangles; and assays to detect various proteins associated with neurodegeneration. Specification, paragraphs 00135 and 00136. Such methods were well known in the art as of the priority date of the instant application. Indeed, a variety of methods of testing compounds for their effect on AD were known in the art as of the priority date of the instant application. The specification cites WO 96/40896, WO 96/40895, and WO 95/11994, each of which describes suitable assays. Specification, paragraph 00130. Furthermore, the specification cites U.S. Patent No. 6,046,381, which also describes various assays for phenomena associated with AD. Accordingly, as of the priority date of the instant application, those skilled in the art were aware of various assays for

phenomena associated with AD.

2b. The Office Action has not established a reasonable basis to question the enablement provided for the claimed invention.

The Office Action stated that neither the specification nor the art at the time of filing provides a nexus between the phenotype of the claimed mouse and a phenomenon associated with AD. The Office Action has provided no evidence or reasoning why a person skilled in the art would doubt that a claimed gene-targeted mouse would exhibit a phenomenon associated with AD. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Indeed, the Office Action acknowledged that "the state of the art provides evidence that apoE, and particularly apoE4, is associated with AD." Office Action, page 8.

The Office Action stated that Baum et al. states that the apoE4 allele increases the risk of AD, but that the mechanism is unclear; and that Baum teaches that in humans, patients with AD with apoE4 have increased amyloid deposition. The Office Action further stated that Dong and Weisgraber ((1996) *J. Biol. Chem.* 271:19053) states that the underlying mechanism(s) as to why apoE4 is a major risk factor for AD is unknown. However, it is well established that Applicants need not understand how an invention works to satisfy the enablement requirement of 35 U.S.C.§112, first paragraph. Thus, any lack of understanding of the underlying mechanism as to why apoE4 is a risk factor for AD is irrelevant to an analysis of enablement of the instant claims.

Notwithstanding the above remarks, and solely in the interest of expediting prosecution, Applicants provide herewith as Exhibit 1 a Declaration of Karl Weisgraber. As described in the Declaration of Karl Weisgraber, a subject gene-targeted mouse exhibits a phenomenon associated with AD. The Declaration of Karl Weisgraber discusses a kainic acid injury model of neurodegeneration. Arg-61 gene-targeted mice (as claimed) and wild-type mice were injected with kainic acid. As discussed in the Declaration of Karl Weisgraber, there was significantly more neurodegeneration in the Arg-61 mice compared to wild-type controls. The results provide further evidence for the fact that the Arg-61 mouse as claimed is a model for neurodegeneration, a phenomenon associated with AD.

Conclusion as to the rejections under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1, 3, 5, 7, 14, 15, and 20-22 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1, 3, 5, 7, 14, 15, and 20-22 were rejected under 35 U.S.C.§112, second paragraph, as allegedly unclear.

The Office Action stated that claims 1, 3, 5, 7, 14, 15, and 20-22 recite, or depend from claims that recite, that the modified endogenous apoE polypeptide comprises a Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4. The Office Action stated that the recitation is unclear because amino acid 61 in human apoE4 is relative to the numbering of the sequence; and stated that it is unclear what a position "equivalent" to amino acid 61 would be. Applicants respectfully traverse the rejection.

As discussed above, the Weisgraber reference provides Figure 1, in which the amino acid sequences of apoE polypeptides from a number of species are aligned with the amino acid sequence of human apoE4. From Figure 1 of the Weisgraber reference, it is clear where amino acid 61 of human apoE4 is. It is also clear from Figure 1 of the Weisgraber reference that, in the amino acid sequence of apoE from every species listed, there is a Thr at a position equivalent to Arg-61 of human apoE4. The Weisgraber reference was available as of the priority date of the instant application; and indeed, the instant specification refers specifically to the Weisgraber reference for guidance. Accordingly, the meaning of "a Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4" is clear, and the claims need not be amended.

Applicants submit that the rejection of claims 1, 3, 5, 7, 14, 15, and 20-22 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(a)

Claims 1, 3, and 5 were rejected under 35 U.S.C.§102(a) as allegedly anticipated by Raffai et al. ((Oct. 31, 2000) *Circulation* Vol. 102, Suppl. II:150, Abstract 729; "the Raffai Abstract").

The Office Action stated that Raffai teaches the site-directed mutagenesis of mouse apoE to introduce an Arg-61 mutation; and gene targeting in ES cells to create mice with an Arg-61 mutation. Applicants respectfully traverse the rejection.

The Raffai Abstract is not available as prior art under 35 U.S.C.§102 against the present application.

Applicants' disclosure of their own work within one year before the application filing date cannot be used against them under 35 U.S.C.§102(a). Therefore, where the applicants are co-authors of a publication cited against their application, the publication may be removed as a reference by submission of a declaration establishing that the article is describing applicants' own work, *i.e.*, that the publication is not "by another." The courts have found that persons involved only with assay and testing are normally listed as coauthors but are not considered co-inventors.[1] Authorship of an article by itself does not raise a presumption of inventorship with respect to the subject matter disclosed in the article. Thus, co-authors may not be presumed to be coinventors merely from the fact of co-authorship.

The situation in the present application is similar to that of *In re Katz*. First, the October31, 2000 publication date of the Raffai Abstract is less than one year before the March 16, 2001 priority date of the instant application. Second, the authors listed on the Raffai Abstract are Raffai, Dong, Tow, Farese, and Weisgraber. Tow is not a co-inventor of the present application. Tow is not an inventor, as he was working under the direction of Weisgraber, and did not contribute to the inventive concept, as explained in the Declaration of Karl Weisgraber under 35 U.S.C.§1.132, provided herewith as Exhibit 3. Accordingly, the Raffai Abstract is the inventors' own work, and as such is not invention "by another."

Therefore, in view of the evidence in the form of the Declaration of Karl Weisgraber under 37 C.F.R.§1.132, the Raffai Abstract is not available as prior art under 35 U.S.C.§102(a) against the present application, as it is derived from the inventors' own work.

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[1] In *In re Katz*, 215 USPQ 14 (CCPA 1982), Katz stated in a declaration that the coauthors of the cited publication, Chiorazzi and Eshhar, "were students working under the direction and supervision of the inventor, Dr. David H. Katz." The court held that this declaration, in combination with the fact that the publication was a research paper, was enough to establish Katz as the sole inventor and that the work described in the publication was his own. In research papers, students involved only with assay and testing are normally listed as coauthors but are not considered co-inventors.

Applicants submit that the rejection of claims 1, 3, and 5 under 35 U.S.C. §102(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§103(a)

Claims 14, 15, and 20-22 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over the Raffai Abstract when taken with Mucke et al. (U.S. Patent No. 6,046,381; "Mucke").

The Office Action stated: 1) the Raffai Abstract teaches site-directed mutagenesis of mouse apoE to introduce an Arg-61 mutation, and gene-targeting in ES cells to create mice with an Arg-61 mutation; 2) the Raffai Abstract does not teach cells isolated from these transgenic mice, and methods of identifying an agent that reduces a phenomenon associated with AD utilizing the mice; 3) Mucke teaches the generation of apoE transgenic mice and methods of utilizing these mice to identify agents that reduce the symptoms of apoE-related pathologies; and 4) Mucke teaches cells isolated from the transgenic animals. The Office Action concluded that, in view of the combined teachings of the Raffai Abstract and Mucke, it would have been obvious for one of ordinary skill in the art to use the transgenic mice comprising an Arg-61 mutation in methods of identifying agents that reduce a phenomenon associated with AD, and to isolate cells from such mice. Applicants respectfully traverse the rejection.

As discussed above, the Raffai Abstract is not available as prior art under 35 U.S.C.§102(a) against the present application. Accordingly, the Raffai Abstract is also not available as prior art under 35 U.S.C.§103(a) against the present application.

The Office Action stated that the Raffai Abstract does not teach cells isolated from these transgenic mice, and methods of identifying an agent that reduces a phenomenon associated with AD utilizing the mice. Mucke cannot cure the deficiency in the Raffai Abstract, because Mucke neither discloses nor suggests a gene-targeted mouse as recited in claim 1 of the instant application. Accordingly, Mucke cannot render any of instant claims 14, 15, and 20-22 obvious.

Applicants submit that the rejection of claims 14, 15, and 20-22 under 35 U.S.C. §103(a) has

been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-222.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 6, 2004

By: _____
Paula A. Borden
Registration No. 42,344

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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